REMARKS

Claims 1-83 were pending in the present application.

Applicants have canceled claims 12-20 and 24-83, without prejudice, as being drawn to non-elected subject matter and amended claim 1, without prejudice. Applicants reserve the right to pursue the deleted subject matter in one or more continuing applications.

Claim 1 has been amended to clarify that which Applicants regard as the invention. Specifically, claim 1 has been amended to recite that the heterologous adenoviral E4 region or portion thereof is inserted into the replication-defective adenovirus in place of nucleic acid sequence encoding open reading frame 6 (ORF6) or nucleic acid sequence encoding the complete adenoviral E4-encoding region. Support for this amendment can be found in the specification, as published as U.S. Patent Application No. 2004/0106194 ("published application"), for example, at paragraph [0016] and original claims 4 and 5.

Claim 84 has been added directed to a specific embodiment where a heterologous gene of interest is inserted into an E1-deleted region. Support for this amendment can be found in the published application, for example, at paragraph [0065].

No new matter has been added by these amendments.

After entry of these amendments, claims 1-11, 21-23 and 84 will be pending in the present application.

Applicants respectfully request entry of the foregoing amendments and consideration of the following remarks.

Claim Rejections – 35 U.S.C. § 103(a)

Claims 1-11 and 21 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Falck-Pedersen (U.S. Patent No. 5,849,561), Lusky (Lusky *et al.*, 1998 *J. Virol.* 72:2022-2032, Li (U.S. Patent No. 7,026,164), Basler (Basler and Horwitz, 1996 *Virol.* 215:165-177), and Mehtali (U.S. Patent No. 6,475,480).

Claims 21-23 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Falck-Pedersen, Lusky, Li, Mehtali and Magede (Magede *et al.*, 2000, J. Virol. 74:2628-2635).

Without admitting to the propriety of the rejection and in an effort to advance prosecution of the present application, Applicants have amended claim 1 to recite that the

heterologous adenoviral E4 region or portion thereof is inserted into the replication-defective adenovirus in place of nucleic acid sequence encoding open reading frame 6 (ORF6) or nucleic acid sequence encoding the complete adenoviral E4-encoding region.

The legal standard and cited references had previously been discussed in the Amendment and Response to Office Action filed on March 6, 2007 ("Amendment").

In response to Applicants' arguments in the Amendment, the Examiner contends that Falck-Pedersen, cited in its entirety, teaches a method involving "cell lines providing E1 and E4 of one serotype [that] would be sufficient to complement an adenovirus of a distinct serotype which is deleted in E4." Applicants respectfully request that the Examiner provide a more detailed citation, as Applicants can find no basis for this in Falck-Pedersen. Moreover, contrary to the Examiner's contention, the replication-deficient adenovirus of Falck-Pedersen is not deficient in E4. Applicant also notes that the claims have been amended to require that the heterologous E4 sequence in inserted into the replication-defective adenovirus in place of the adenovirus E4 ORF6 or entire E4 region, implying that at a minimum the native E4 ORF6 of the replication-defective adenovirus is deleted.

The Examiner maintains that there is a motivation to combine the teachings of Falck-Pedersen and Mehtali because Falck-Pedersen discusses the functional interaction between serotypes is absolutely conserved, and the essential gene products of the E1 and E4 regions should be derived from the same serotype and Mehtali discloses E4 regions that are in *cis*. The Examiner had previously contended in the Office Action mailed November 15, 2006 that one of skill in the art would have been motivated to combine the teachings given the knowledge by Lusky that deletion of E1 is sufficient to impair expression of viral genes.

First, Applicants respectfully submit that there is no motivation to combine the teachings of Falck-Pedersen and Mehtali because Lusky teaches away from the present invention. "A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention." See MPEP § 2141.02, emphasis added (citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)). Lusky teaches that multiply deleted adenovirus vectors have clear advantages over E1 only deleted vectors, including (1) prevention of recombinant-competent adenovirus through recombination events, and (2) an improved safety profile due to

the oncogenic potential of the E4 ORF6. See Lusky, pg. 2031, col. 1, last paragraph. Given this teaching, there would be a strong motivation to use the teachings of Falck-Pedersen (producing a virus using a cell line providing the functions of E1 and E4 either stably integrated in the genome or having one of the functions provided with a helper virus; see Falck-Pedersen, col. 9, lines 29-41) to produce $E1^-$ $E4^-$ adenovirus vectors as the necessary E4 function is provided in *trans*. In view of the teachings of Lusky, one would not be motivated to provide E4 ORF6 function in *cis*. Instead, one would have been motivated to create replication-defective adenovirus vectors with minimal E4 regions and strongly consider supplying at least E4 ORF6 in *trans*.

Second, Applicants respectfully submit that there is no motivation to combine the references because the desirability of the combination has not been shown. The knowledge that Lusky teaches that deletion of E1 is sufficient to impair expression of viral genes does not appear to provide a clear line of reasoning for a motivation and Applicants respectfully request that the Examiner expand on her reasoning. On its face, the Examiner appears to be combining Falck-Pedersen and Methali merely because they teach the claimed elements. "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." See MPEP § 2143.01 (citing *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)).

Falck-Pedersen provides a perfectly acceptable means of producing replication-defective adenovirus in complementing cells. It is unclear why it would be desirable to provide E4 function in *cis* especially in view of the trade-offs involved. "Trade-offs often concern what is feasible, not what is, on balance, desirable. Motivation to combine requires the latter." See *Winner Intern. Royalty Corp. v. Wang*, 202 F.3d. 1340, 53 USPQ2d 1580 (Fed. Cir. 2000). The major benefit of Falck-Pedersen and the present invention is eliminating the need for separate complementing cells for each adenoviral strain that one wishes to produce. See Falck-Pedersen, col. 7, line 65 to col. 8, line 2. For example, in order to grow Ad7 (serogroup B), one would typically need a complementing cell line that produces E1 product from a serogroup B adenovirus instead of 293 cells which produce E1 products from Ad5 (serogroup C). Falck-Pedersen solved the problem of needing separate complementing cells for different serogroups by proving E4 product in *trans* (either expressed in the genome or from a helper virus) from the same serogroup as the complementing cell. See Falck-Pedersen, col. 8, lines 3-59. The present

invention obviates the need for separate complementing cells by providing E4 product from the same serogroup as the complementing cell in *cis*. In the present invention, a heterologous adenoviral E4 region encoding at least ORF6 is inserted into a replication-defective vector. This means that every adenovirus vector (of a different serogroup than the E1 product supplied by the complement cell) must be customized to include the E4 region from the same serogroup as the E1 product in the complementing cell. Furthermore, as discussed above, Lusky teaches that it is not desirable to have ORF6 present in the adenovirus vector and that multiply deleted vectors such as $E1^{-}$ $E4^{-}$ are preferred. These trade-offs must be balanced against the benefits obtained with the present invention. The primary benefit of the present invention is the ability to use existing and settled adenoviral E1-complementing cell lines (such as PER.C6™ and 293) based on Ad5. However, in view of the numerous E1/E4 complementing cells available at the time of the invention (such as those disclosed in Falck-Pedersen; Abramsen et al., 1997, J. Virol. 71:8946-8951; and U.S. Pat. No. 6,270,996; all of which are cited in the Background of the Invention), the trade-offs weigh heavily against a motivation for the present invention.

For the above reasons, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. 103.

CONCLUSION

Applicants believe the claims are in condition for allowance. An early indication of the same is requested. The Examiner is invited to contact Applicants' Attorney at the telephone number given below, if such would expedite the allowance of this application.

Respectfully submitted,

Date: 10/12/07

By: _____

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